Remarks

Claims 1-9, 12 and 13 were pending. Claims 6, 9, 12 and 13 were withdrawn from consideration; Claims 7-9 have been rejoined to Group I.

Claims 1-5, 7 and 8 have been rejected under 35 U.S.C. 112, second paragraph. Claims 1, 2, 4 and 7 have been amended in accordance with the Examiner's suggestions. Withdrawal of the rejections is requested.

Claims 1, 2, 7 and 8 have been rejected under 35 U.S.C. 102(b) as anticipated by Clay *et al.* (2001) and/or obvious under 35 U.S.C. 103(a). Applicants respectfully submit that the presently claimed invention is not anticipated or suggested by the cited art.

The present claims have been amended to recite a monopotent megakaryocyte progenitor. The claims have also been amended to recite a population of cells that is negative for a panel of lineage markers, which set of markers include CD19 and GPA.

As discussed in the specification at paragraphs 85-92, the inventors prospectively searched for cells that could give rise to only megakaryocytes and extensively tested their differentiation potentials in several *in vitro* and *in vivo* assays. The MKPs isolated here meet all criteria for megakaryocyte-committed progenitors and therefore provide a definitive proof of the existence of these monopotent progenitors.

The cells isolated by Clay *et al.* differ from the presently claimed cells in their cell surface phenotype and in their developmental potential. Applicants note that the present claims have been amended to recite a lineage panel, which lineage panel was not used for selection in the cited prior art reference.

On page 1985 of Clay et al., it is stated that "in some experiments, $CD9^{+}CD41^{+}$ cells were sorted according to CD41 expression; gates D and C (Figure 3) corresponded to $CD41^{mid/low}$ and $CD41^{high}$ cells, respectively."

Clay *et al.* analyzed the sorted cells as follows:

> In contrast to the other myeloid progenitors, when $CD34^{+}CD41^{-}$ bone marrow cells were sorted into $CD9^{low}$, $CD9^{mid}$, and $CD9^{high}$ subpopulations, CFU-MK were highly enriched in the $CD9^{high}$ population (Figures 4, 5). Only a small proportion of CFU-MK was detected in the $CD9^{low}$ fraction, and an intermediate proportion was detected in the $CD9^{mid}$ fraction. As indicated earlier, a small fraction of the $CD34^{+}CD9^{+}$ cells expresses the CD41 antigen. Therefore, we sorted $CD9^{high}$ and $CD9_{mid}$ cells according to their CD41 expression level (Figure 3). The proportion of CFU-MK was 4-fold higher in the $CD9^{mid}CD41^{neg}$ fraction (gate B) than in the $CD9^{mid}CD41^{mid/low}$ population (gate D) (24 ± 2 and 6 ± 1,

respectively, for 10_4 plated cells). In contrast, $CD9^{high}CD41^{high}$ (gate E) only gave rise to a small number of differentiated megakaryocytic clusters.

When EPO was added to these cultures, BFU-E/MK mainly arose from the differentiation of the $CD9^{mid}$ cells (21 ± 16 for 10^4 plated cells) compared to $CD9^{high}$ (7 ± 4 for 10^4 plated cells). Few BFU-E/MK were detected in the $CD9^{low}$ fraction and even then only in some experiments (data not shown).

One of skill in the art will conclude from the teachings of Clay et al. that the cell population of $CD34^+CD41^+CD9^+$ cells that are unsorted for lineage markers comprise only a small number of progenitor cells that give rise to differentiated megakaryocyte clusters, which population also comprises progenitor cells for mixed erythroid colonies (BFU-E/MK), and therefore is not a population of monopotent megakaryocyte progenitor cells.

Applicants therefore submit that the phenotypic and functional characterization of the prior art cell population differs from the characteristics of the presently claimed cell population. One of skill in the art would not be motivated to pursue a monopotent megakaryocyte progenitor cell in the cell populations defined by Clay et al., as the $CD34^+CD41^+CD9^+$ population was stated to contain only a small number of differentiated megakaryocyte clusters.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-5 have been rejected under 35 U.S.C. 102(b) as anticipated by, or obvious over Akashi *et al* (2000) Nature 404:193-197. Applicants respectfully submit that the cited art does not anticipate or suggest the presently claimed invention. Akashi *et al.* teach a cell population termed the megakaryocyte/erythroid progenitor (MEP), which cell population has the cell surface phenotype of being $CD34^-$ and thus is distinguished from the present progenitor cell population.

Akashi *et al.* teach a cell population termed the granulocyte monocyte committed progenitor cell (GMP), which cell population is not a progenitor for megakaryocytes, and which does not give rise to megakaryocyte colonies.

The third cell population described by Akashi *et al.* is the common myeloid progenitor. It is noted that this cell population is not characterized with respect to expression of CD9 or CD41. Applicants will endeavor to provide the Examiner with experimental data regarding the expression of these markers on this and other cell populations. However, the CMP progenitor is readily distinguished from the cell population set forth in the present claims, as the common myeloid progenitor CMP cells gives rise to various types of myeloerythroid colonies, including CFU-GEMMeg, burst-forming unit-erythroid (BFU-E), CFU-megakaryocytes (CFU-Meg), CFU-granulocyte/ macrophage (CFU-GM), CFU-granulocyte (CFU-G) and CFU-macrophage

(CFU-M). Therefore this cell population differs from the monopotent, committed megakaryocyte progenitor of instant claims.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-5 have been rejected under 35 U.S.C. 102(a) as anticipated by, or obvious over NaNakorn *et al.* (2002) J. Clin. Invest. 109:1579-1585. Applicants respectfully submit that the cited art does not anticipate or suggest the presently claimed invention. The cell populations described by Nanakorn *et al.* are identical to the Akashi *et al.* cell populations, which for the reasons described above are distinguished from the cell population of the instant claims.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-5 have been rejected under 35 U.S.C. 102(e) as anticipated by, or obvious over Weissman *et al.*, U.S. Patent no. 6,465,247 or U.S. Patent Application Publication 2002/0086422. Applicants respectfully submit that the cited art does not anticipate or suggest the presently claimed invention. The cell populations described by Nanakorn *et al.* are identical to the Akashi *et al.* cell populations, which for the reasons described above are distinguished from the cell population of the instant claims.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-278.

Respectfully submitted,
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